

Amendments to the Claims

The listing of claims will replace all prior versions, and listings of claims in the application.

1. (currently amended) A method for determining the effect of a substance on ~~characteristics of neurodegenerative disease~~ sequestration, uptake or accumulation of amyloid in brain cells, said method comprising:

- (A) exposing brain cells to a condition that modulates integrins or integrin receptors in said cells,
- (B) maintaining said cells for a time sufficient to induce ~~one or more characteristics of a neurodegenerative disease~~ sequestration, uptake or accumulation of amyloid in said cells,
- (C) adding said substance before, during and/or after said exposing or maintaining; and
- (D) determining whether the presence of said substance has an effect on ~~one or more of said characteristics~~ sequestration, uptake or accumulation of amyloid.

2. (cancelled) The method of claim 1 wherein said characteristics are selected from the group consisting of:

- (1) sequestration of A β ,
- (2) accumulation of A β ,
- (3) uptake of A β ,
- (4) lysosomal dysfunction,
- (5) microglia activation, and
- (6) changes in cathepsin D content.

3. (currently amended) The method of claim 2 1, wherein ~~at least one of said characteristics~~ sequestration, uptake or accumulation of amyloid increases.

4. (original) The method of claim 3, wherein said increase is at least about 10% compared to a control.
5. (currently amended) The method of claim 2 1, wherein at least one of said ~~characteristics~~ sequestration, uptake or accumulation of amyloid decreases.
6. (original) The method of claim 5, wherein said decrease is at least about 10% compared to a control.
7. (original) The method of claim 1, wherein the brain cells are in the form of a brain slice.
8. (original) The method of claim 7, wherein the brain slice is a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, or a cortex slice.
9. (withdrawn) The method of claim 1 wherein said brain cells are *in vivo*.
10. (withdrawn) The method of claim 1, wherein the brain cells are from a non-human transgenic animal.
11. (withdrawn) The method of claim 10, wherein said non-human transgenic animal comprises a human apolipoprotein E4 gene.
12. (withdrawn) The method of claim 10 wherein both alleles of an endogenous apolipoprotein E gene of the non-human transgenic animal are ablated.
13. (original) The method of claim 1, wherein said brain cells in step (A) are cultured in a medium that comprises an antagonist or modulator of an integrin.
14. (original) The method of claim 13 wherein said antagonist or modulator of integrin is a neutralizing or function blocking antibody for integrin subunits wherein said subunits are selected from the consisting of: alpha1, alpha2, alpha3, alpha4, alpha5, alpha6, alpha7, and alpha8, beta1, beta2, beta3, beta4, beta5, beta6, beta7 and beta8.

15. (original) The method of claim 13, wherein said antagonist or modulator of integrin comprises a compound selected from the group consisting of RGD, RGDS (SEQ. ID. No.1), GRGDS (SEQ. ID. No.2), GRGDTP (SEQ. ID. No.4) and GRGDSP (SEQ. ID. No.3), mimetics thereof, echistatin, trilavin, disintegrins and snake venom.

16. (currently amended) The method of claim 2 1, wherein the amount of; sequestration of amyloidA β , accumulation of amyloid A β , uptake of amyloidA β , ~~lysosomal dysfunction, levels of cathepsin D or microglia activation~~ is determined visually.

17. (currently amended) The method of claim 2 1, wherein the amount of; sequestration of amyloidA β , accumulation of amyloid A β , uptake of amyloidA β , ~~lysosomal dysfunction, change of cathepsin D content or microglia activation~~ is measured using a capture reagent.

18. (currently amended) The method of claim 16, wherein the capture reagent is an antibody that binds to amyloid A β , ~~lysosomes, Cathepsin D or a microglia element~~.

19. (currently amended) The method of claim 1 wherein said cells are apolipoprotein E deficient brain cells or apolipoprotein E4 containing brain cells cultured in a medium which selectively increases sequestration of and/or accumulation of and/or uptake of amyloid A β , and/or lysosomal dysfunction, and/or microglia activation in the brain cells, wherein the brain cells comprise an increased amount of sequestration of and/or accumulation of and/or uptake of amyloidA β , and/or lysosomal dysfunction, and/or microglia activation compared to a control.

20. (withdrawn) A method of obtaining brain cells having characteristics of neurodegenerative disease comprising:

- (A) culturing brain cells,
- (B) exposing said brain cells to a condition that modulates integrins or integrin receptors in said cells, and

- (C) maintaining said cells or brain tissue for a time sufficient to induce one or more characteristics of a neurodegenerative disease in said cells.

21. (withdrawn) The method of claim 20, wherein said characteristics are selected from the group consisting of:

- (1) sequestration of A β ,
- (2) accumulation of A β ,
- (3) uptake of A β ,
- (4) lysosomal dysfunction,
- (5) microglia activation and
- (6) changes in cathepsin D content.

22. (withdrawn) The method of claim 21, wherein at least one of said characteristics increases.

23. (withdrawn) The method of claim 22, wherein said increase is at least about 10% compared to a control.

24. (withdrawn) The method of claim 21, wherein at least one of said characteristics decreases.

25. (withdrawn) The method of claim 24, wherein said decrease is at least about 10% compared to a control.

26. (withdrawn) The method of claim 20, wherein the brain cells are in the form of a brain slice.

27. (withdrawn) The method of claim 26, wherein the brain slice is a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, or a cortex slice.

28. (withdrawn) The method of claim 20, wherein the brain cells are from a non-human transgenic animal.

29. (withdrawn) The method of claim 28, wherein said non-human transgenic animal comprises a human apolipoprotein E4 gene.

30. (withdrawn) The method of claim 28 wherein both alleles of an endogenous apolipoprotein E gene of the non-human transgenic animal are ablated.

31. (withdrawn) The method of claim 20, wherein said brain cells in step A are cultured in a medium that comprises an antagonist or modulator of an integrin.

32. (withdrawn) The method of claim 31 wherein said antagonist or modulator of integrin is a neutralizing or function blocking antibody for integrin subunits wherein said subunits are selected from the group consisting of: alpha1, alpha2, alpha3, alpha4, alpha5, alpha6, alpha7, and alpha8, beta1, beta2, beta3, beta4, beta5, beta6, beta7 and beta8.

33. (withdrawn) The method of claim 31, wherein said antagonist or modulator of integrin comprises a compound selected from the group consisting of RGD, RGDS (SEQ. ID. No.1), GRGDS (SEQ. ID. No.2), GRGDTP (SEQ ID NO.4) and GRGDSP (SEQ. ID. No.3), mimetics thereof, echistatin, triflavin, disintegrins and snake venom.

34. (withdrawn) The method of claim 20 wherein said cells are apolipoprotein E deficient brain cells or apolipoprotein E4 containing brain cells cultured in a medium which selectively increases sequestration of and/or accumulation of and/or uptake of A β , and/or lysosomal dysfunction, and/or microglia activation in the brain cells, wherein the brain cells comprise an increased amount of sequestration of and/or accumulation of and/or uptake of A β , and/or lysosomal dysfunction, and/or microglia activation compared to a control.

35. (withdrawn) Brain cells obtained by the method of claim 20.

36. (original) The method of claim 1 wherein the brain cells are contacted with a compound that modulates integrins or integrin receptors prior to contacting with the substance whose effect is being determined.

37. (original) The method of claim 1, wherein the brain cells are contacted simultaneously with the compound that modulates integrins and/or integrin receptors and the substance whose effect is being determined.

38. (withdrawn) An *in vitro* method for increasing at least one or more characteristics of neurodegenerative disease in brain cells, wherein said characteristics are selected from the group consisting sequestration of A β , accumulation of A β , uptake of A β , lysosomal dysfunction, changes in cathepsin D content and microglia activation, said *in vitro* method comprising:

- (A) exposing brain cells in culture to a condition that modulates integrins or integrin receptors in said cells wherein said modulation results in increase in characteristics of neurodegenerative disease in said cells, and
- (B) maintaining said cells in culture for a time sufficient to increase one or more characteristics of a neurodegenerative disease in said cells.

39. (withdrawn) The method of claim 38, wherein at least one of said characteristics increases.

40. (withdrawn) The method of claim 39, wherein said increase is at least about 10% compared to a control.

41. (withdrawn) The method of claim 38, wherein at least one of said characteristics decreases while other characteristics increase.

42. (withdrawn) The method of claim 41, wherein said decrease is at least about 10% compared to a control.

43. (withdrawn) The method of claim 38, wherein the brain cells are in the form of a brain slice.

44. (withdrawn) The method of claim 43, wherein the brain slice is a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, or a cortex slice.

45. (withdrawn) The method of claim 38, wherein the brain cells are from a non-human transgenic animal.

46. (withdrawn) The method of claim 45, wherein said non-human transgenic animal comprises a human apolipoprotein E4 gene.

47. (withdrawn) The method of claim 45 wherein both alleles of an endogenous apolipoprotein E gene of the non-human transgenic animal are ablated.

48. (withdrawn) The method of claim 38, wherein said brain cells in step (A) are cultured in a medium that comprises an antagonist of an integrin.

49. (withdrawn) The method of claim 48 wherein said antagonist or modulator of integrin is a neutralizing or function blocking antibody for integrin subunits wherein said subunits are selected from the group consisting of: alpha1, alpha2, alpha3, alpha4, alpha5, alpha6, alpha7, and alpha8, beta1, beta2, beta3, beta4, beta5, beta6, beta7 and beta8.

50. (withdrawn) The method of claim 48 wherein said antagonist or modulator of integrin comprises a compound selected from the group consisting of RGD, RGDS (SEQ. ID. No.1), GRGDS (SEQ. ID. No.2), GRGDTP (SEQ. ID. No.4) and GRGDSP (SEQ. ID. No.3), mimetics thereof, echistatin, triflavins, disintegrins and snake venom.

51. (withdrawn) The method of claim 38 wherein said cells are apolipoprotein E deficient brain cells or apolipoprotein E4 containing brain cells cultured in a medium which selectively increases sequestration of and/or accumulation of and/or uptake of A β , and/or lysosomal dysfunction, and/or microglia activation in the brain cells, wherein the brain cells comprise an increased amount of sequestration of and/or accumulation of and/or uptake of A β , and/or lysosomal dysfunction, and/or microglia activation compared to a control.

52. (withdrawn) The brain cells produced by the method of claim 38.

53. (withdrawn) Brain cells *in vitro*, wherein the brain cells have been treated with a compound that modulates integrins and/or integrin receptors, thereby producing characteristics of a brain afflicted with a neurodegenerative disease or an aged brain.

54. (withdrawn) The brain cells of claim 53, wherein said characteristics are selected from the group consisting of sequestration of A β , accumulation of A β , uptake of A β , lysosomal dysfunction, changes in cathepsin D content and microglia activation.

55. (withdrawn) A method for alleviating the symptoms of disease states having at least one of the following characteristics selected from the group consisting of intracellular uptake of amyloid protein, amyloid accumulation and plaque formation, said method comprising:

- (A) administering to a patient in need thereof a composition comprising an effective amount of an NMDA receptor antagonist, and
- (B) determining the effectiveness of treatment with said composition,
- (C) increasing or decreasing the composition based on the determinative testing, and
- (D) alleviating symptoms of the disease.

56. (withdrawn) A pharmaceutical composition comprising a compound capable of sufficiently inhibiting the activity of the NMDA receptor in an amount effective to alleviate one or more symptoms of disease states associated with at least one characteristic selected from the group consisting of abnormal accumulation, abnormal molecular organization of amyloid protein and amyloid plaques and said composition also includes a suitable carrier or pharmaceutical excipient.

57. (withdrawn) The pharmaceutical composition of claim 56 wherein said compound is selected from a group consisting of magnesium, ketamine, dextromethorphan, amantadine, dexanabinol, AP3, AP5, AP6, AP7, 4C3HPG, 4CPG, CGS 19755, chlorophenylglutamic acid, CPP, MK-801, PCP, ibogaine, noribogaine,

ifenprodil, flupirtine, selfotel, D-CPP-ene, procyclidine, trihexyphenidyl, CP-101606, CP-98113, GVI150526, AR-R15896AR, NPS 1506, NPC 12626, LY274614, LY 2835959, SDZ 220-040, SDZ 220-040, SDZ 220-581, SDZ 221-653 and memantine.

58. (withdrawn) A method for inhibiting the intracellular accumulation of amyloid comprising:

- (A) contacting brain cells with a glutamate receptor antagonist and
- (B) determining whether the intracellular accumulation of amyloid is inhibited.

59. (currently amended) A method for determining the effect of a substance on inhibition of ~~characteristics of neurodegenerative disease~~ sequestration, uptake or accumulation of amyloid in brain cells, said method comprising:

- (A) exposing brain cells to a condition that modulates integrins or integrin receptors in said cells,
- (B) maintaining said cells for a time sufficient to induce one or more characteristics of a neurodegenerative disease in said cells,
- (C) adding said substance before, during and/or after said exposing or maintaining; and
- (D) determining whether the presence of said substance inhibits one or more of said characteristics.

60. (cancelled) The method of claim 59 wherein said characteristics are selected from the group consisting of:

- (1) sequestration of A β ,
- (2) accumulation of A β ,
- (3) uptake of A β ,
- (4) lysosomal dysfunction,
- (5) microglia activation and
- (6) changes in cathepsin D content.

61. (currently amended) The method of claim ~~60~~ 59, wherein at least one of said ~~characteristics~~ sequestration, uptake or accumulation of amyloid decreases.

62. (original) The method of claim 61, wherein said decrease is at least about 10% compared to a control.

63. (original) The method of claim 60, wherein the brain cells are in the form of a brain slice.

64. (original) The method of claim 63, wherein the brain slice is a hippocampal slice, an entorhinal cortex slice, an entorhinohippocampal slice, a neocortex slice, a hypothalamic slice, or a cortex slice.

65. (withdrawn) The method of claim 59 wherein said brain cells are *in vivo*.

66. (withdrawn) The method of claim 59, wherein the brain cells are from a non-human transgenic animal.

67. (withdrawn) The method of claim 66, wherein said non-human transgenic animal comprises a human apolipoprotein E4 gene.

68. (withdrawn) The method of claim 67 wherein both alleles of an endogenous apolipoprotein E gene of the non-human transgenic animal are ablated.

69. (original) The method of claim 59, wherein said brain cells in step A are cultured in a medium that comprises an antagonist or modulator of an integrin.

70. (original) The method of claim 69 wherein said antagonist or modulator of integrin is a neutralizing or function blocking antibody for integrin subunits wherein said subunits are selected from the group consisting of: alpha1, alpha2, alpha3, alpha4, alpha5, alpha6, alpha7, and alpha8, beta1, beta2, beta3, beta4, beta5, beta6, beta7 and beta8

71. (original) The method of claim 69, wherein said antagonist or modulator of integrin comprises a compound selected from the group consisting of RGD, RGDS (SEQ. ID. No.1), GRGDS (SEQ. ID. No.2), GRRDT (SEQ. ID. No.4) and GRGDSP (SEQ. ID. No.3), mimetics thereof, echistatin, triflavin, disintegrins and snake venom.

72. (currently amended) The method of claim ~~60~~ 59, wherein the amount of; sequestration of amyloidA β , accumulation of amyloid A β , uptake of amyloid A β , ~~lysosomal dysfunction, changes in cathepsin D content or microglia activation~~ is determined visually.

73. (currently amended) The method of claim ~~60~~ 59, wherein the amount of; sequestration of amyloidA β , accumulation of amyloidA β , uptake of amyloidA β , ~~lysosomal dysfunction or microglia activation~~ is measured using a capture reagent.

74. (currently amended) The method of claim 73, wherein the capture reagent is an antibody that binds to amyloidA β , ~~lysosomes, Cathepsin D or a microglia element~~.

75. (original) The method of claim 59 wherein said cells are apolipoprotein E deficient brain cells or apolipoprotein E4 containing brain cells.

76. (withdrawn) The method of claim 55 wherein said determining is done using brain imaging techniques.

77. (withdrawn) The method of claim 76 wherein said brain imaging techniques are MRI or PET.

78. (withdrawn) The method of claim 55 wherein said determining is done using EEG or cognitive tests.

79. (new) A method for determining the effect of a substance on lysosomal dysfunction, microglia activation or changes in cathepsin D content in brain cells, said method comprising:

- (A) exposing brain cells to a condition that modulates integrins or integrin receptors in said cells,
- (B) contacting said cells with amyloid
- (C) maintaining said cells for a time sufficient to induce lysosomal dysfunction, microglia activation or changes in cathepsin D content in said cells,
- (D) adding said substance before, during and/or after said exposing or maintaining; and
- (E) determining whether the presence of said substance has an effect on lysosomal dysfunction, microglia activation or changes in cathepsin D content in said cells .